EXHIBIT A

The effects of a low frequency sonic waveform on osteoarthritis: A pilot study

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Key Words: Sonic waveform; Alternative therapy; Osteoarthritis; Pain; Range of motion

Running Title: Effects of low frequency sound on osteoarthritis

ABSTRACT

Objective: To evaluate the effects of a low frequency sonic waveform on osteoarthritis (OA).

Methods: Adults with OA were recruited from local advertisements to participate in a quasi-experimental pre-test, post-test, 24 hour post-test design using the Cassone transducer. Range of motion (ROM) was measured for the wrist, knee, and hip using goniometry, and pain was assessed using a visual analog scale.

Results: Significant differences were demonstrated between pre and post measures for 4 of the 8 areas investigated. Significant differences were also demonstrated for 4 of the 8 areas investigated between the pre and 24-hour measures. Participants demonstrated significant decreases in pain between pre and post measures as well as between pre and 24-hour measures.

Conclusion: The results of this pilot study suggest that use of the Cassone transducer as an alternative form of therapy appears to improve ROM while overall decreasing pain.

Figure Legends

Figure 1 The mean ($\pm$ SE) ROM outcome measures for the right extremities before treatment (Pre), immediately following treatment (Post), and 24-hour post treatment (24-hour). The asterisk (*) indicates that Post ROM was significantly greater than Pre ($P < 0.05$), while the double asterisk (**) indicates that 24 hour ROM was significantly greater than Pre ($P < 0.05$).

Figure 2 The mean ($\pm$ SE) ROM outcome measures for the left extremities before treatment (Pre), immediately following treatment (Post), and 24-hour post treatment (24-hour). The asterisk (*) indicates that Post ROM was significantly greater than Pre ($P < 0.05$), while the double asterisk (**) indicates that 24 hour ROM was significantly greater than Pre ($P < 0.05$).

Figure 3 The mean (+ SE) Pain outcome measures before treatment (Pre), immediately following treatment (Post), and 24-hour post treatment (24-hour). The asterisk (*) indicates that Post Pain was less than Pre ($P < 0.05$), while the double asterisk (**) indicates that 24 hour Pain was less than Pre ($P < 0.05$).

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INTRODUCTION

Osteoarthritis (OA), referred to as degenerative joint disease, is the most common joint disease in the world, affecting as many as 80% of persons older than 75 years of age (1). Although the risk for OA increases with age, radiographic features may be noted in as many as 90% of those as young as age 40 in weight bearing joints (2). The details of the causes of OA are still unknown.

The most commonly involved joints are the knees, hips, cervical and lumbar spine, proximal and distal interphalangeal joints, first carpometacarpal joint, metatarsophalangeal joints, and less commonly the wrists. Involvement in these joints may be unilateral initially, but usually becomes bilateral as the disease progresses (3, 4). Pain is the leading symptom of OA (5) and typically becomes more persistent and severe as the disease progresses. Methods of treating pain in OA include surgical and pharmacologic interventions, range of motion and isometric exercises, and nontraditional therapies. Surgical interventions, although costly, have afforded patients pain relief and satisfactory range of motion (6). Apart from surgical measures, treatment is typically aimed at alleviating pain, swelling, muscle tightness, and restoration of mobility. Pharmacologic treatment relies primarily on the use of NSAIDS. Given the concern regarding the side effects of these drugs, close monitoring of the disease and treatment progression is necessary (7). Chondroprotective drugs, such as mucopolysaccharides, have also been reported to decrease OA pain with intra-articular administration and are currently being evaluated in both animal models and patients (8).

Non-pharmacologic interventions are the first line treatment of all patients with OA (7, 9). Many studies have demonstrated the efficacy of physical exercise in reducing arthritis pain and disease activity (10-14). However, significant decreases in pain are usually not achieved by

exercises prescribed for patients with OA (5). Therapeutic heat and cold, electrotherapy, therapeutic ultrasound, acupuncture, hydrotherapy, and spa treatment are widely used. Although many of these interventions have proven effective in reducing pain, improving joint function, and increasing quality of life, results have been inconsistent (15-22). It is apparent that the effects of biophysical actions of many therapeutic interventions on pain and function are partially understood and have not been fully established.

These studies show the need for new therapeutic regimens with the ability to effectively decrease the pain inflicted by this disease (23). Many different types of alternative treatments such as herbal remedies, supplements, and diet therapies have also been used in attempts to treat OA. However, according to several studies, alternative treatments are not substantiated by medical research and have sometimes proven to be very costly to the patient. Therapeutic modalities that can help to reduce pain without the untoward side effects of medications may prove to be extremely beneficial in the management of painful OA. Recent anecdotal evidence has supported the use of a new technology and treatment. A sonic waveform in a specific low frequency range (audible sound) has been used in people experiencing various diseases or injuries and has appeared to alleviate or diminish pain, increase range of motion (ROM), and improve function.

Effects of Sound. Sound waves are a form of vibration and are divided into three groups: infrasound, audible sound, and ultrasound. Infrasound ranges from 1-16 Hz (inaudible), audible sound ranges from 16-20,000 Hz, and therapeutic ultrasound (inaudible) is any sound wave with a frequency above 20,000 Hz (24). Ultrasound has been shown to have thermal and non-thermal effects on the body. Although many studies involving the use of ultrasound exist, there are relatively few studies concerned with the physiological effects on humans of infrasound

exposure (25). Audible sound is, in contrast to all other environmental factors, continuously present in the external environment. Audible sound has been shown to have physiological effects on the body and its metabolic processes by activating subcortical neural systems. By activating these systems, the cardiovascular, metabolic, endocrine, reproductive, and neurological functions of the body may be altered (26).

A study performed by Jensen and Rasmussen (27) exposed mice to a sound at 800 Hz and an intensity between 120-123 decibels. Exposing the mice to the sound for 3 hours daily for 30 days was shown to impair interferon production and limit the inflammatory response. They found that the stress caused by the sound induced hyperactivity of the pituitary-adrenocortical axis, which they believe to be the cause of the inhibition of the inflammatory response. Henkin and Knigge (28) showed similar results, exposing rats to 220 Hz at 130 decibels for up to 48 hours. Their research showed that this intense sound doubled the output of corticosterone in 30 minutes and tripled the output in 60 minutes. Billewicz-Stankiewicz and Krepinska-Urban (29) also reported an inhibition of the inflammatory response after exposing rats to 2 hours of 86 dB sound (sound and vibration).

In 1981, Borg investigated the physiological and pathogenic effects of sound (30). His study involved exposing rats to environmental noise for 10 hours per day for the life span of the rat at levels of 85 and 105 decibels. His findings showed that there are no significant changes in blood pressure, body weight, water consumption, life span, or disease panorama. The only potential risks he determined were hearing loss and lesions to the sensory cells of the inner ear. These were related to exposure level, duration of exposure, and the strain of the animal. Borg concluded that exposure to "pseudo-constant neutral" sound at this intensity poses no threat to

the health of humans except for a potential loss of hearing sensitivity in those studies that use excessively high decibel levels for prolonged periods of time.

Recent anecdotal reports have been received demonstrating that audible sound in a particular range below 2000 Hz has had astounding effects on reducing the pain associated with OA. Currently, there are no studies that have addressed the use of audible sound as a treatment for OA. Due to the paucity of research, there is a need to investigate the relationship between audible sound in this frequency range and its effect on disease states. Information derived from empirically measuring outcomes such as pain and ROM might help to further elucidate the mechanisms involved with low frequency audible sound. Using new technology, the purpose of this study was to examine the effects of a low frequency sonic waveform on OA.

METHODS

Participants. This quasi-experimental research study utilized a one group pretest-posttest design. Adult volunteers were recruited through local newspaper advertisements. Prior to advertising, university institutional review board approval was obtained. Interested participants attended a 30-minute information session prior to the study to determine their eligibility, which included a previously diagnosed OA condition, English speaking, no previous sonic therapy treatments, no implanted devices, and being non- pregnant. Informed oral and written consents were obtained from eligible participants. Participants were informed not to change their normal daily routines.

Equipment. The treatment was performed using a new technology called the Cassone Transducer. It consists of a metal cylinder with a slot extending its axial length and includes an arrangement of hollow piezoelectric cylinders, placed one atop another, to form a piezoelectric stack. The stack is tightly contained within a resilient metal sleeve and vibrate together as a unit when electric pulses are applied across the cylinders. Ceramic material bonded to the tube's

inner wall and having piezoelectric characteristics provides the driving mechanism in achieving wall vibrations.

The sleeve gap is coextensive, and aligned, with the gap in the piezoelectric stack. Together, the combination of the piezoelectric stack and the sleeve, form a horseshoe, capable of vibrating like a tuning fork. The width of the gap opening (its circumferential length) affects the resonant frequency of the transducer, as does the piezoelectric wall thickness and the diameter of the stack. The piezoelectric cylinder is polarized radially (i.e., from the interior surface of the piezoelectric ceramic cylinder to its outside surface). The electrical pulses needed to cause vibrations of the cylinder are, thus, applied between the interior of the piezoelectric stack and the exterior of the steel sleeve.

Design frequencies at which the tube vibrates are directly related to the wall material, its thickness, the diameter, and to some extent, the width of the gap. A key facet of this technology is the efficiency in which electrical energy is converted to mechanical movement. The transducer is capable of operating at high efficiency, while resonating at a specified frequency. Additionally, it resonates with an omnidirectional beam pattern. The machine emits a moderately loud sound, exposing participants to approximately 76 to 78 decibels of sound (without the headphones on), which is within OSHA standards. Use of the headphones effectively reduces the decibels of sound to which the participant is exposed. The frequency used is this study is below 2000 Hz. We are unable to disclose the actual frequency range used in this study as it is considered proprietary at this time due to patent pending. The machine does not currently have FDA approval.

Visual Analog Pain Scale. A visual analog pain scale was utilized to determine OA pain perception before the intervention, after the intervention, and 24-hours later. The scale was a

standard 100-millimeter line ranging from 0 (no OA pain) to 10 (worst OA pain ever). Participants were asked to mark through the line in accordance with how much pain was felt at that time. Researchers were able to accurately measure the amount of pain indicated with the use of a millimeter ruler. The visual analog scale has been widely used in measuring the subjective nature of pain intensity. Researchers have shown that when examiners use the same pain scales when assessing and reassessing patient's perceived pain, valid and reliable results have been achieved (31-33).

Goniometry. Many organizations including the American Medical Association and the American Academy of Orthopaedic Surgeons and researchers have adopted the 0 to 180-degree goniometric notation system as an objective measurement of joint positions (34, 35). Riddle performed an inter-rater reliability on the effects of goniometric measurement of the shoulder (34). He concluded that goniometric passive measurement can be highly reliable and valid when taken by a single therapist. Based on this principle, a single therapist performed pre-treatment and post-treatment passive range of motion (ROM) measurements using the 0 to 180 degree goniometric notation system at the wrist and metacarpal phalangeal joints bilaterally. To avoid any bias of the therapist performing the measurements, a different individual recorded the values of the measurements as stated by the therapist. Goniometric measurements were performed pre-treatment, post-treatment, and 24-hours post-treatment.

Procedure. On the day of the study prior to the intervention, participants completed a brief background questionnaire along with a visual analog pain scale. An on-site goniometric examination for bilateral ROM of the hand and wrist, knee, and hip was performed. Following these pre-measurements, participants were escorted to a room for the treatment. Up to six participants were treated at one time and were seated facing the generator in a circular fashion

approximately one foot away from the generator column. Participants were asked to wear headphones through which relaxation music could be controlled by individual volume dials. The treatment consisted of sitting in a chair for 25 minutes during which time the sonic wave generator was turned on. Post measurements were taken for the same variables following the treatment and follow-up measurements were taken at 24 hours.

Data Analysis. Visual analog and goniometric data were analyzed using one-way repeated measures ANOVA (SPSS, version 10.0). When the omnibus F-ratio was significant, planned comparisons were conducted with the alpha level set at 0.05 using the main effects comparison option available via SPSS. The planned comparisons of interest were the comparisons of ROM and pain between measurement times.

RESULTS

Seven males and 14 females with a mean age of 68.1 $\pm$12.4 years participated in the study. Comparisons of pre, post, and 24-hour data for all 21 participants for each of the body areas examined are summarized in Figures1 through 3. Body areas measured were bilateral wrist extension, wrist flexion, knee flexion, and hip flexion. The data were separated into right and left outcome measures as well as pre, post, and 24-hour measures of pain.

The means of all participants demonstrated increased ROM changes over a 24-hour period for all of the areas examined. Significant differences were demonstrated between pre and post measures for 4 of the 8 areas investigated: right hip flexion ($p = 0.004$), left wrist flexion, ($p = 0.002$), left hip flexion ($p = 0.000$), and left knee flexion ($p = 0.010$). Pre to 24-hour measures demonstrated significant differences for 4 of the 8 areas investigated: right wrist flexion ($p = 0.004$), right hip flexion ($p = 0.001$), left wrist flexion ($p = 0.019$), and left hip flexion ($p = 0.000$).

Participants demonstrated significant decreases in pain between pre and post measures ($p = 0.000$) as well as between pre and 24-hour measures ($p = 0.007$).

DISCUSSION

The present study was designed to evaluate the effects of a low frequency sonic waveform on OA and to determine whether or not it could be a useful treatment for sufferers of this disease. This was conducted in order to provide a necessary background for further research with this device for OA and other disease states. All of the participants in this study showed improvement over a 24-hour period. We also demonstrated that exposure to the sonic waves at the designated frequency significantly increased the ROM in several of the body areas examined immediately post treatment as well as 24 hours post treatment. Additionally, the intervention significantly decreased pain immediately post treatment and 24-hours post treatment. No untoward side effects were noted. We are unable to corroborate the results obtained with other studies because of the novelty of this intervention.

Studies involving infrasound (i.e. under 16 Hz) have yielded diverging results and have mostly explored the effects of on the auditory and non-auditory systems (30, 36-39). Although therapeutic US has achieved recognition as a suitable method to treat a wide variety of musculoskeletal conditions, those conducted on individuals suffering with OA have been unable to distinguish its effects from sham therapy (20). The characteristics of low frequency sonic waveforms involved in physiological reactions aside from the auditory system are largely unknown. No studies to date have examined the effects of full body exposure to low frequency audible sound in this range for any disease state.

Our study has several limitations. First, we realize this study is subjected to recruitment bias. All of the participants in this study responded to a solicitation to participate in a trial of

sonic waveform treatment for OA. Second, although the participants stated they all suffered with OA and that they had been previously diagnosed with the condition, we did not use an independent physician to confirm this diagnosis. It is possible that some participants may have had other conditions that mimicked OA and were unintentionally used in our study. Third, in order to prove a treatment efficacious, the prescription of treatment for OA should follow general guidelines of medical therapy. Due to the novelty of this treatment, indications, dosage regimens, and other therapeutic effects have yet to be determined. Fourth, the small number of participants and the lack of a control group limit the current study. Lastly, we also realize that the music may have had a relaxing effect on the participants, which may have served to decrease pain immediately post treatment. However, this does not explain the continued decrease in pain 24 hours later.

Despite the obvious limitations, we believe that this study adds pertinent information regarding the use of an alternative therapy for patients experiencing OA. No attempt was made to elucidate a mechanism of action at this time. Future research on other disorders such as rheumatoid arthritis are currently being conducted using this device. Based on the promising results of this study, we are using double blind, randomized control designs in an effort to distinguish the efficacy of this intervention from that of a placebo effect. In conclusion, the results of this pilot study suggest that use of the Cassone transducer as an alternative form of therapy appears to improve ROM while decreasing pain. These results are sufficiently positive to warrant more definitive research concerning empirical data as well as attempting to establish a mechanism of action using this device.

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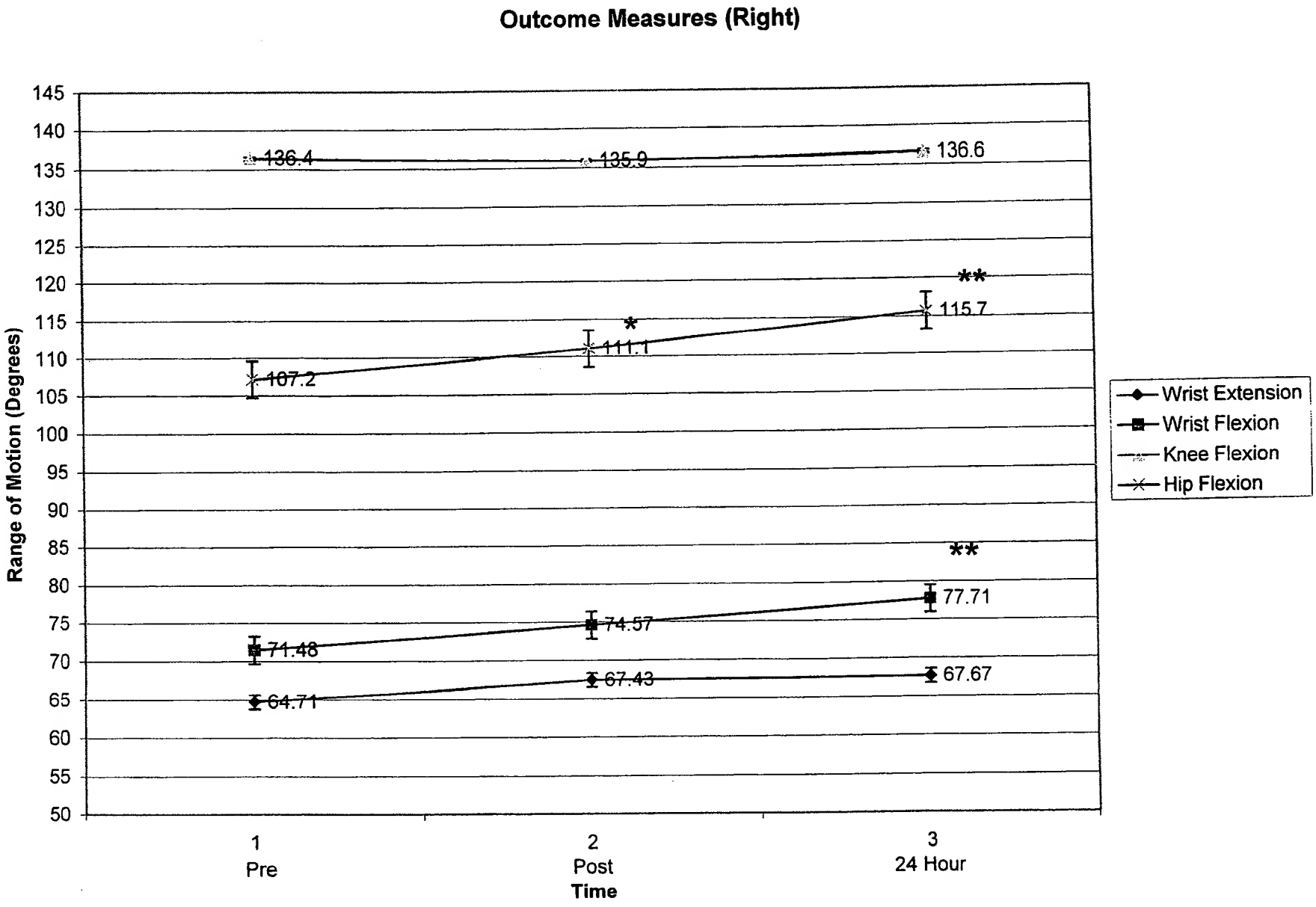
Outcome Measures (Right)
Range of Motion (Degrees)
145
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130
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120
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110
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90
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80
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70
65
60
55
50
136.4
135.9
136.6
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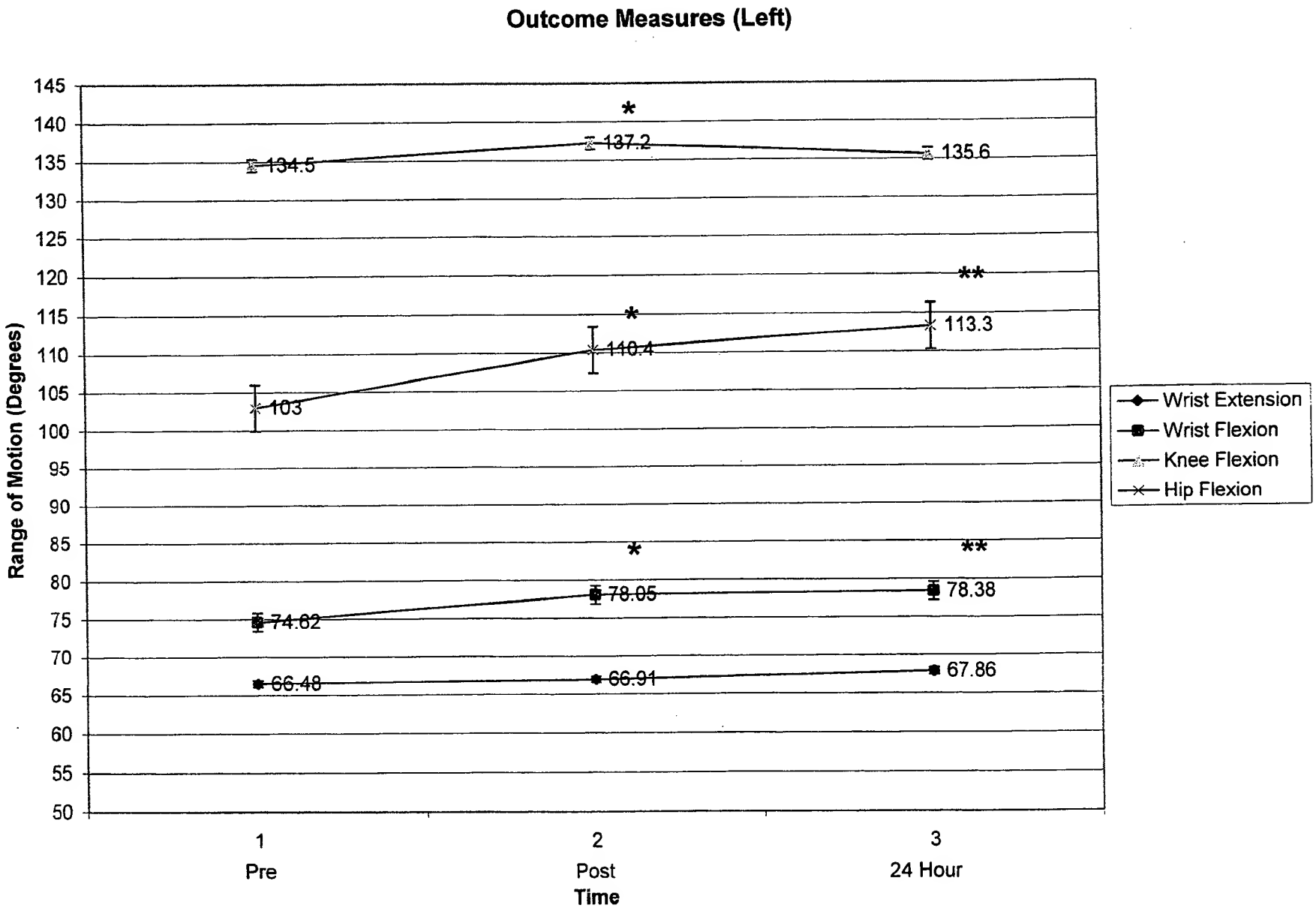
*
115.7
111.1
107.2
**
77.71
74.57
71.48
67.43
67.67
64.71
1
Pre
2
Post
3
24 Hour
Time
Wrist Extension
Wrist Flexion
Knee Flexion
Hip Flexion


Outcome Measures (Left)
Range of Motion (Degrees)
145
140
135
130
125
120
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105
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80
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70
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60
55
50
134.5
137.2
135.6
103
110.4
113.3
74.62
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66.48
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67.86
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1
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24 Hour
Time
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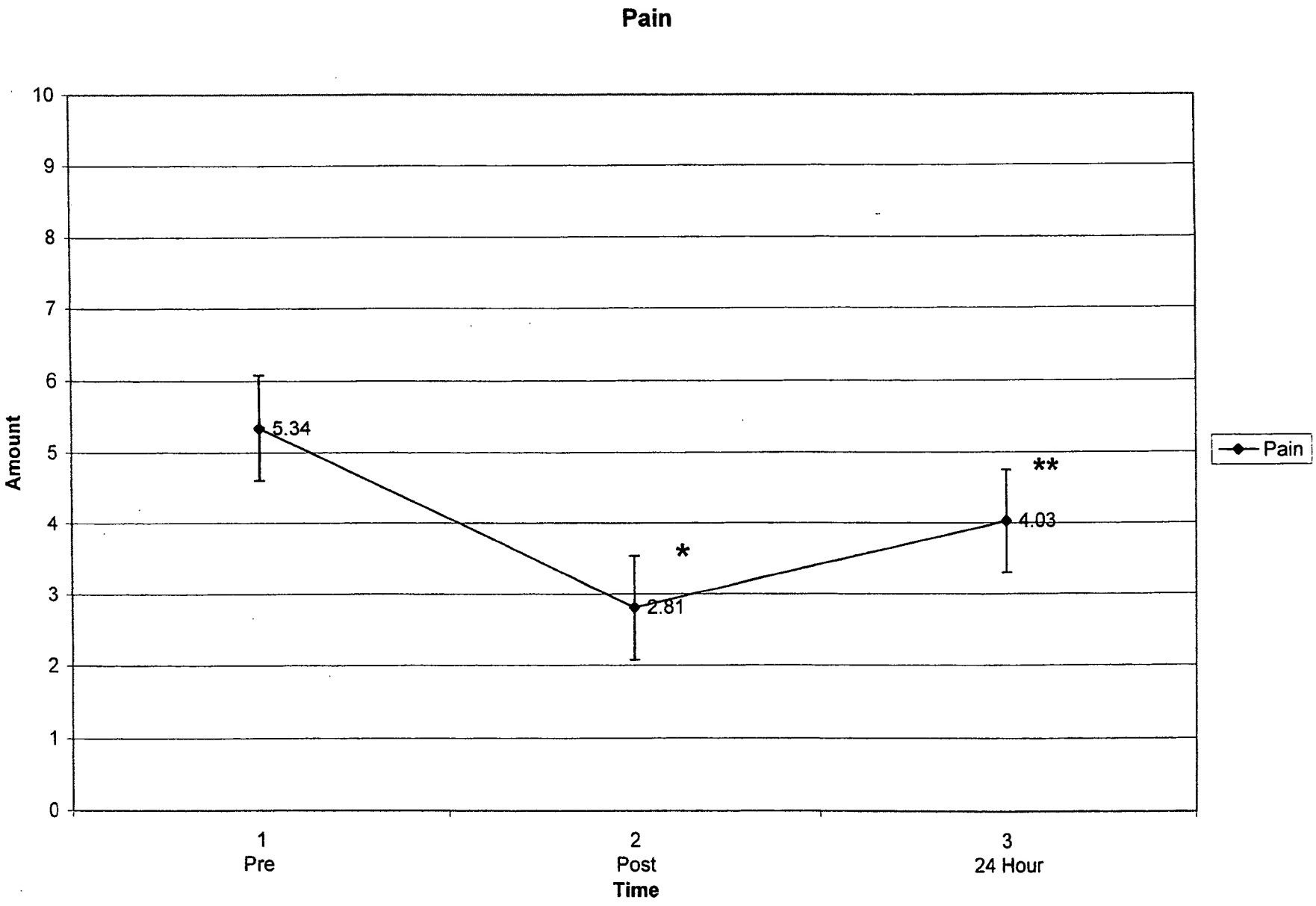
Wrist Flexion
Knee Flexion
Hip Flexion


Pain
10
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Amount
5.34
2.81
4.03
*
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1
Pre
2
Post
3
24 Hour
Time
Pain

We would like to acknowledge the assistance provided by Alphonse Cassone and his facility in which this study was conducted. Mr. Cassone is the inventor of the Cassone Transducer, a patented technology. Mr. Cassone has applied for various medical patents utilizing the Cassone Transducer.